REMARKS

As a preliminary matter, applicants acknowledge with appreciation the Examiner's indication that claims 1-14, 23-28, and 38 are free of art and therefore allowable.

With the instant amendment, claims 23, 29, and 39 have been canceled; claims 1, 27, 30-32, 38, and 40 have been amended; and claims 41-44 are new. Support for the new claims is found in the specification at: page 18, lines 18 and 21-23 (claim 41); page 19, lines 24-25 (claim 42); page 19, lines 18-19 (claim 43); and page 18, lines 6-7 (claim 44). Upon entry of this amendment, the following claims will be pending in this application: claims 1-14, 24-28, 30-33, 35, 36, 38, and 40-44.

All of the objections and rejections set forth in the Office Action under reply are addressed in part by the amendments set forth above and the comments and arguments that follow.

CLAIM OBJECTIONS

The Examiner has objected to claims 23, 27, and 38 as having informalities. In response, claim 23 has been canceled and claims 27 and 38 have been amended in accordance with the Examiner's suggestions. With these amendments, claims 23, 27, and 38 are rendered moot.

CLAIM REJECTION – 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-14, 23-33, 35, 36, and 38-40 stand rejected under 35 U.S.C. § 112, first paragraph, as indefinite. In response, applicants have amended claims 1, 29, and 31 to delete the term "alveolitis" and have canceled claim 23. With these amendments, this rejection is rendered moot.

CLAIM REJECTIONS – 35 U.S.C. § 103(a); CLAIMS 29, 31, 33, 39 AND 40

Claims 29, 31-33, 39, and 40 stand rejected under 35 U.S.C. § 103(a) as obvious over Fischer et al. in view of Pezzuto et al., Goodman & Gilman's Ninth Edition, and American Drug Index, Facts and Comparisons. This rejection is rendered moot for canceled claims 29 and 39 and is respectfully traversed for claims 31-33 and 40, as amended.

When establishing a *prima facie* case of obviousness, the Office must show that the cited prior art references, either singly or in combination, suggest the desirability of the claimed subject matter. *In re Deminski,* 796 F.2d 436, 230 USPQ 313 (Fed. Cir. 1986). To establish a *prima facie* case of obviousness, two basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. On this matter, even if a primary prior art reference could be readily modified to form the claimed invention, the mere fact that the prior art can be so

modified does not by itself make the modification obvious unless the prior art suggests the desirability of the modification. *In re Laskowski,* 871 F.2d 115, 10 USPQ2d 1397 (Fed. Cir. 1989). Second, there must be a reasonable likelihood of success in view of the prior art. *Brown V. Williamson Tobacco Corp. v. Phillip Morris, Inc.,* 229 F.3d 1120 (Fed. Cir. 2000).

A prerequisite to making a finding on section 103 obviousness is determining what is prior art, in order to consider whether the differences between the subject matter sought to be patented and the prior art such that the subject matter as a whole would have been obvious at the time of the invention to one of ordinary skill in the art. *In re Clay*, 966 F.2d 656, 23 USPQ2d 1058 (Fed. Cir. 1992). If a cited reference is not analogous art, it has no bearing on the obviousness of the patent claim. *Jurgens v. McKasy*, 927 F.2d 1552, 18 USPQ2d 1031 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 902 (1991). Under the two step test for determining whether a prior art reference is nonanalogous and thus not relevant in determining obviousness, it must be determined: (i) whether the reference is "within the field of the inventor's endeavor"; and (ii) if not, whether the reference is "reasonably pertinent to the particular problem with which the inventor was involved." *In re Deminski*, 796 F.2d 436, 230 USPQ 313 (Fed. Cir. 1986). The claimed invention and the reference patents are within the same field of endeavor if they have essentially the same function. *Id.*

It is well-established that an obviousness analysis that relies upon the applicant's disclosure rather than the prior art reference is improper as being based upon an impermissible hindsight reconstruction. *In re Deuel,* 51 F.3d 1551, 1558 (Fed. Cir. 1995). Similarly, the combination of elements from nonanalogous sources, in a manner that reconstructs the applicant's invention only with the benefit of hindsight, is insufficient to present a *prima facie* case of obviousness. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992).

Lastly, it must be remembered that the *prima facie* case is a procedural tool which, as used in patent examination, means not only that the evidence of the prior art would reasonably allow the conclusion the Examiner seeks, but also that the prior art compels such a conclusion if the applicant produces no evidence or argument to rebut it. *In re Spada,* 911 F.2d 705 (Fed. Cir. 1990). If examination at the initial stage does not produce a *prima facie* case of unpatentability, then without more, the applicant is entitled to a grant of the patent. *In re Oetiker,* 977 F.2d 1443 (Fed. Cir. 1992).

The present invention as recited in independent claim 31 relates to a pharmaceutical formulation for the treatment of alveolar inflammatory disease, such as chronic obstructive pulmonary lung disease ("COPD") and interstitial lung disease ("ILD"), comprising a first active agent selected from the group consisting of resveratrol, pharmacologically acceptable salts, esters, amides, prodrugs or analogs thereof, and combinations of any of the foregoing; and a second active agent selected from the group consisting of

leukotriene receptor inhibitors and macrolide antibiotics, and combinations thereof. In dependent claim 32, a third active agent, a long-acting β adrenergic agonist is recited in combination with a carrier suitable for pulmonary administration. The purpose of the third active agent as recited to effect deeper delivery of the first and second active agents into the lungs when the formulation is inhaled (*see*, specification, p. 18, ll. 3-6 and 10-18).

Fischer et al. teaches the use of chloride-activating agents, such as flavones and/or isoflavones, for the treatment of diseases characterized by defective chloride transport in epithelial tissues, such as primarily cystic fibrosis, and chronic bronchitis and asthma as well (col. 6, ll. 58-63). It is known that cystic fibrosis affects the secretory epithelia of a variety of tissues, reducing the ability of epithelial cells in the airways, pancreas, and other tissues to transport chloride ions, and accompanying sodium and water (col. 1, ll. 24-30). The principal clinical manifestation of cystic fibrosis is the resulting respiratory disease, characterized by airway obstruction due to the presence of thick mucus in the airway surfaces. In cystic fibrosis, defective chloride transport is due to a mutation in a chloride channel known as the cystic fibrosis transmembrane conductance regulator ("CFTR"). In addition to flavones and isoflavones, Fischer et al. also teaches that resveratrol, ascorbic acid, ascorbate salts, and dehydroascorbic acid may also enhance chloride transport in epithelial cells (col. 2, ll. 49-54). Fischer et al. teaches that certain flavones and isoflavones, as well as other polyphenolic compounds, such as ascorbic acid and resveratrol, are capable of stimulating CFTR-mediated chloride transport in epithelial tissues (col. 6, ll. 64-67; col. 7, ll. 2-3; col. 11, ll. 47-67).

Fischer et al. does ***not*** disclose combining resveratrol with the leukotriene receptor inhibitors or macrolide antibiotics of independent claim 31 or the long acting β adrenergic agonists of dependent claim 32. Accordingly, Fischer et al. alone does not render obvious the claimed invention.

Pezzuto et al. does not correct the deficiencies of Fischer et al. Pezzuto et al. teaches pharmaceutical formulations of resveratrol useful for preventing or treating *skin conditions, disorders, or diseases associated with or caused by inflammation, sun damage, or natural aging* (col. 1, ll. 19-24; col. 10, ll. 45-50). Pezzuto et al. does not teach or suggest that resveratrol may be useful for the treatment of inflammatory disorders that are ***not*** associated with surface skin.

The Examiner cites Pezzuto et al. for the addition of anti-inflammatory agents or antibiotics to resveratrol and cites specifically, col. 10, ll. 16-19 and 45-50 for support (Office Action, p.5, 1st full para.). Applicants have carefully reviewed Pezzuto et al. and note that the only mention of anti-inflammatory agents and antibiotics in this patent document are the two single brief references found at col. 10, ll. 17 and 19, respectively, that "anti-inflammatory agents" and "antibiotics" may be included in the disclosed topical skin formulations (*see*, col. 7, l. 47 to col. 10, l. 15, which discloses the embodiments

of the topical skin formulations). No specific anti-inflammatory agents or antibiotics are disclosed therein.

As noted above in the discussion of the relevant law, a prior art reference in a nonanalogous is irrelevant to an obviousness analysis. In the instant rejection, applicants submit that Pezzuto et al. is in fact nonanalogous art. The claimed invention is clearly directed to the treatment of internal disorders that affect respiration. By contrast, Pezzuto et al. is directed to the treatment of skin diseases. One of ordinary skill in the art attempting to treat respiratory disorders would not be compelled to turn to teachings on skin disorders to find additional active agents to incorporate in treatments for alveolar inflammatory disease. Thus, it follows that Pezzuto et al. is *not* within applicant's field of endeavor. Further, it must be noted that the purpose of the claimed invention is *not* the *use* of resveratrol for the treatment of *any* disorder; the purpose of the claimed invention is the *treatment* of alveolar inflammatory disease with a pharmaceutical formulation comprising resveratrol as the primary active agent. Hence, Pezzuto et al. also fails to be reasonably pertinent to the problem that applicants are addressing. Accordingly, applicants submit that Pezzuto et al. is not a proper prior art reference for this obviousness analysis because it constitutes *nonanalogous art*. *See, In re Deminski, supra.*

Turning to Goodman & Gilman's, this reference also does not correct the deficiencies of Fischer et al. and Pezzuto et al. While Goodman & Gilman's does teach the use of long-acting β-adrenergic agonists for the treatment of asthma, no mention is made of leukotriene inhibitors or macrolide antibiotics as suitable drugs for the treatment of asthma. Accordingly, the combination of Fischer et al. in view of Pezzuto et al. and Goodman & Gilman's does not teach or suggest the claimed invention.

Lastly, the disclosure in the American Drug Index that salmeterol xinoate is a long-acting bronchodilator does not cure the deficiencies of Fischer et al., Pezzuto et al., and Goodman & Gilman's as it provide not teaching that will render obvious the claimed combination of independent claim 31.

As the foregoing discussion demonstrates, the hypothetical combination of Fischer et al. in view of Pezzuto et al., Goodman & Gilman's, and the American Drug Index fails to teach or suggest the invention of independent claim 31 *et seq*. Accordingly, because the claimed invention is not rendered obvious by Fischer et al. in view of Pezzuto et al., Goodman & Gilman's, and the American Drug Index, applicants respectfully request reconsideration and withdrawal of this rejection.

CLAIM REJECTIONS – 35 U.S.C. § 103(a); CLAIMS 30, 35, AND 36

Claims 30, 35, and 36 stand rejected under 35 U.S.C. § 103(a) as obvious over Fischer et al. in view of Pezzuto et al., Goodman & Gilman's, the American Drug Index, and Remington's Pharmaceutical Sciences, 15th Ed. This rejection is respectfully traversed.

With the cancellation of claim 29, claim 30 has been amended to depend ultimately from claim 31. Because the foregoing discussion demonstrates that independent claim 31 is not rendered obvious by the hypothetical combination of Fischer et al. in view of Pezzuto et al., Goodman & Gilman's, and the American Drug Index, the additional teachings of Remington's with respect to inhalers will not serve to render these dependent claims obvious.

Because claims 30, 35, and 36 are not obvious over the cited art, applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

The foregoing discussion demonstrates that independent claim 31 *et seq.* is not obvious over the cited references. Accordingly, applicants respectfully request reversal of all outstanding rejections for this application. Because all outstanding issues for this application have been fully addressed, upon entry of this amendment and upon reversal of the outstanding rejections set forth in the Office Action under reply, applicants respectfully submit that they are entitled to a patent grant on the invention set forth in the instant patent application. *See, In re Oetiker, supra.*

If the Examiner has any questions regarding this response that may be addressed by way of a phone call or e-mail communication, she is welcome to contact the undersigned attorney at 650-330-4913 or at canaan@reedpatent.com.

Respectfully submitted,

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